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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,538	09/15/2003	Peter S. Lu	020054-000211US	5609

20350 7590 10/17/2007

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	
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10/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/663,538	LU ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *7,13,14 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-12 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-20* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendices A and B*.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 02 August 2007 has been entered in full. Claims 1, 2, 4, 6, 15 are amended.

This application contains claims 7, 13, 14, and 18-20 drawn to an invention nonelected with traverse in the reply filed on 20 November 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-6, 8-12, and 15-17 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pages 4-5 of the previous Office Action (02 February 2007) are *withdrawn in part* in view of the amended specification (02 August 2007). Please see section on Specification, below.

2. The objections to claims 1-4, 6, and 15 at page 5 of the previous Office Action (02 February 2007) are *withdrawn in part* in view of the amended claims (02 August 2007). Please see section on Claim Objections, below.

3. The rejection of claims 1-3, 6, 8-12, and 15-17 under 35 U.S.C. § 112, first paragraph (scope of enablement) for recitation of nucleic acid variants as set forth at pages 12-14 of the previous Office Action (02 February 2007) is *withdrawn* in view of the amended claims (02 August 2007).

4. The rejection of claims 1-6, 8-12, and 15-17 under 35 U.S.C. § 112, first paragraph (written description) as set forth at pages 18-20 of the previous Office Action (02 February 2007) is *withdrawn* in view of the amended claims (02 August 2007).

5. The rejection of claim 5 under 35 U.S.C. § 112, first paragraph (Deposit Rules) as set forth at pages 20-22 of the previous Office Action (02 February 2007) is *withdrawn* in view of Applicant's declaration of 02 August 2007.

6. The rejection of claims 1-6, 8-12, and 15-17 under 35 U.S.C. § 112, second paragraph as set forth at page 22 of the previous Office Action (02 February 2007) is *withdrawn* in view of the amended claims (02 August 2007).

7. The rejection of claims 1, 15-16 under 36 U.S.C. § 102(b) as set forth at pages 22-23 of the previous Office Action (02 February 2007) is *withdrawn* in view of the amended claims (02 August 2007).

8. The rejection of claims 8-12 and 17 under 35 U.S.C. § 103(a) as set forth at pages 23-25 of the previous Office Action (02 February 2007) is *withdrawn* in view of the amended claims (02 August 2007).

Sequence Compliance

The Applicant's response to the Notice to Comply with Sequence Listing Requirements under 37 CFR §1.821 (02 August 2007 has been considered and is found persuasive. Therefore, the requirements set forth in the Notice to Comply (02 February 2007) are *withdrawn.*

Specification

9. The disclosure is objected to because of the following informalities:

9a. The specification refers to Figures which were deleted in the amendment of 16 January 2004. Please see, for example, pages 25, 45, 47, 68, 113, 114, 115, 125. The basis for this objection is set forth at page 4 of the previous Office Action (02 February 2007).

It is noted that at page 1 of the response of 02 August 2007, Applicant indicates that Applicant is reconsidering re-introducing these figures into the application.

Appropriate correction is required.

Claim Objections

10. Claims 4, 6 and 15 are objected to because of the following informalities:

10a. Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 (upon which claim 4 depends) and claim 4 both recite a polynucleotide encoding SEQ ID NO: 2.

10b. Claims 6 and 15 use the acronym "CLASP-2" without first defining what they represent in the independent claims. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym. The basis for this objection is set forth at page 5 of the previous Office Action (02 February 2007).

Appropriate correction is required.

Claim Rejections - 35 USC § 101 and § 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-6, 8-12, and 15-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation. The basis for this rejection is set forth at pages 5-11 of the previous Office Action (02 February 2007).

Applicant's arguments (02 August 2007), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts at page 2 of the Response that knowledge of how an invention works is not needed for patentability. Applicant indicates that it is enough for Applicants to have identified that CLASP-2 is involved in such processes, and to have identified the disease states that ultimately correlate with CLASP-2 dysfunction.

Applicant's arguments have been fully considered but are not found to be persuasive. Although knowledge of how an invention works is not needed for patentability, the invention must be supported by either a credible, specific, and substantial asserted utility or a well established utility. In the instant application, the specification does not disclose any methods or working examples the indicate the CLASP-2 polynucleotide and polypeptide are involved in any processes, such as T cell activation, regulation of T cell and B cell interactions, and in the organization, establishment, and maintenance of the "immunological synapse" (including signal transduction, cytoskeletal interactions, and membrane organization) (pg 22, lines 1-7; pg 21, lines 1-5). Since significant further research would be required of the skilled artisan to determine

how the claimed polypeptide is involved with the above-mentioned activities, the asserted utilities are not substantial. Since the utility is not presented in mature form and significant further research is required, the utility is not substantial.

The specification also does not disclose any disease states associated with a mutated, deleted, or translocated CLASP-2 gene (SEQ ID NO: 1) or protein (SEQ ID NO: 2). The specification does not disclose which disorders are associated with altered levels of the CLASP-2 gene or protein. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

(ii) At page 3 of the Response, Applicant argues that post-filing date work has confirmed the involvement of CLASP-2 in immune response, especially T-cell activation. Applicant indicates that multiple publications have shown that CLASP-2 (called Zizimin 1 or DOCK9) interacts with and activates a rho-family GTPase called cdc42 (Meller et al. 2002). Applicant also submits that activated cdc42 promotes cytoskeletal polarization of T cells in response to contact with antigen-presenting cells (Stowers et al. 1995). Applicant concludes that the role of CLASP-2 in promoting T cell activation is of clear relevance to immunological diseases such as immune system disorders, allergic reactions, organ rejection, etc.

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant indicates that CLASP-2 is also known as Zizimin 1 or DOCK9, which has been shown to interact with cdc42. However, according to the Examiner's sequence search of 18 December 2006, the CLASP-2 amino acid sequence of SEQ ID NO: 2 is only 94.0% identical to

Zizimin1/DOCK9 (see sequence alignment attached to the instant Office Action as Appendix A). Additionally, the CLASP-2 nucleic acid sequence of SEQ ID NO: 1 is only 73.8% identical to the Zizimin1 nucleic acid sequence (see sequence alignment attached to the instant Office Action as Appendix B). Thus, it is not clear how Applicant has concluded that CLASP-2 is Zizimin1/DOCK9. From the sequence search performed by the PTO, it seems that CLASP-2 and Zizimin1/DOCK9 are different proteins.

Additionally, although the specification of the instant application teaches that CLASP-2 expression levels decrease at 1 hour, 2 hours, and 4 hours after T cell activation (pg 125, lines 4-14), it cannot be determined if this decrease is a significant difference as compared to T-cells that have not been activated. If the decrease in CLASP-2 expression is not significant between the two cell types, then this utility is not specific because the skilled artisan would not be able to distinguish activated T-cells from inactivated T-cells. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial. Applicant is encouraged to submit any evidence under 37 C.F.R. 1.132 that would indicate a significant difference between the expression of CLASP-2 in activated and inactivated T-cells.

(iii) At the bottom of page 3 of the Response, Applicant contends that the very striking similarity between CLASP-1 and CLASP-2 (Figure 5) imparts substantial credibility to Applicant's assertion that CLASP-2 (like CLASP-1) is involved in T-cell activation. Applicant asserts that there is no basis for the Examiner to argue to the contrary or to assert that Applicant's disclosed utility of CLASP-2 is neither specific nor substantial.

Applicant's arguments have been fully considered but are not found to be persuasive. The truth, or credibility, of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not specific or substantial. In the previous Office Action of 02 February 2007, the Examiner made a *prima facie* showing that the claimed invention lacks utility and provided sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. The assertion that the disclosed CLASP-2 polynucleotide has biological activities similar to protein family members having a role in T cell activation is not specific or substantial in the absence of supporting evidence, because the relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p.

438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48). Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different

molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Thus, the specification fails to support the asserted credible, specific and substantial utility of T cell activation.

(iv) At page 4 of the Response, Applicant argues that the Office Action's allegation that it is necessary to completely characterize the nature of CLASP-2's involvement in T cell activation is incorrect. Applicant adds that inhibitors can be identified by the relatively simple *in vitro* binding assays disclosed in the specification. Applicant states that it is not necessary to have a complete understanding of underlying mechanisms to identify inhibitors of CLASP-2 activity, nor to perform trials of such identified inhibitors in cellular or animal models for activity in protecting against cell death. Applicant indicates that usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development and cites *in re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

Applicant's arguments have been fully considered but are not found to be persuasive. The asserted utilities put forth by Applicant and the specification of the instant application are credible, but not specific or substantial. The asserted utility of screening for activators/inhibitors can be performed with any polypeptide. The specification also discloses nothing specific or substantial about the ligands, agonists/antagonists, and binding proteins that are identified by these methods. Substantial further research is required to determine the usefulness of agonists,

antagonists isolated in this manner. Since these asserted utilities are also not present in mature form, so that they could be readily used in a real world sense, the asserted utilities are not substantial. Furthermore, the fact patterns of the case cited by the Applicant and of the instant rejection are significantly different, and the court decision is not binding with regard to the instant rejection. Although, as discussed *in re Brana,* that pharmaceutical inventions necessarily include further research and development, it is clear from the instant specification that the polypeptide described therein is what is termed an "orphan protein" in the art. This is a protein whose cDNA has been isolated because of its similarity to known proteins. There is little doubt that, after complete characterization, this DNA and protein, may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility.

12. Claims 1-6, 8-12, and 15-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial

asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth at pages 11-12 of the previous Office Action (02 February 2007).

Applicant's arguments (02 August 2007), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant states that a specific and substantial asserted utility, as described above. Specifically, since Applicant has not provided evidence to demonstrate that the CLASP-2 polynucleotide and polypeptide have a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. It is noted that the instant specification is required to teach one skilled in the art how to make and use the polypeptide encoded by the claimed polynucleotides.

13. However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 10-12 would remain rejected under 35 U.S.C. § 112, first paragraph. The basis for this issue is set forth at pages 14-17 of the previous Office Action (02 February 2007) and is reiterated herein below.

The Examiner has interpreted claims 10-12 as reading on isolated host cells, as well as host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy. The specification of the instant application teaches that CLASP-2 gene can be expressed in transgenic animals and any technique known in the art may be used to introduce a CLASP-2 transgene into animals to produce the founder lines of transgenic animals (pg 66-67). However, there are no methods or working examples disclosed in the instant application whereby

a multicellular animal with the incorporated CLASP-2 gene of SEQ ID NO: 1 is demonstrated to express the CLASP-2 peptide. There are also no methods or working examples in the specification indicating that a multicellular animal has CLASP-2 "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Additionally, for example, the specification discloses that two possible techniques used to introduce a CLASP-2 transgene into animals include pronuclear microinjection and gene targeting in embryonic stem cells (pg 66, lines 28-31). However, the literature teaches that the production of transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome which may disrupt or interfere with critical endogenous gene expression (Wigley et al. Reprod Fert Dev 6: 585-588, 1994). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even rarer than random events. Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events in microinjected embryos, it would have required undue experimentation for the skilled artisan to have made any and all transgenic

non-human animals according to the instant invention. Furthermore, regarding gene targeting in embryonic stem cells, the specification does not provide guidance for identifying and isolating embryonic stem cells or for identifying other embryonal cells which are capable of contributing to the germline of any animal. At the time of filing, Campbell et al. teaches that, "in species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species...However, as yet there are not reports of any cell lines which contribute to the germ line in any species other than mouse" (Campbell et al. Theriology 47(1): 63-72, 1997; see pg 65, 2nd paragraph). Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells which can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

The specification also discloses that nucleic acids encoding the CLASP-2 polypeptide can be used for gene therapy (pg 62-65). However, the specification does not teach any methods or working examples that indicate a CLASP-2 nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the CLASP-2 nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has

been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express a CLASP2 nucleic acid into the cell of an organism. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express a CLASP-2 nucleic acid in the cell of an organism or be able to produce a CLASP-2 protein in that cell. (Please note that this issue could be overcome by amending the claims to recite, for example, "An isolated host cell...").

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the CLASP-2 protein and to introduce and express a CLASP-2 nucleic acid in a cell of an organism for therapy; the lack of direction/guidance presented in the specification regarding how to introduce a CLASP-2 nucleic acid in the cell of an organism to be able produce that CLASP-2; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of making transgenic animals and of transferring genes into an organism's cells; and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
12 October 2007

Bridget E. Bunner

BRIDGET E. BUNNER
PRIMARY EXAMINER

Appendix A

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<!--StartFragment-->RESULT 3
DOCK9_HUMAN
ID   DOCK9_HUMAN     STANDARD;      PRT;  2069 AA.
AC   Q9BZ29; Q5JUD4; Q5JUD6; Q5T2Q1; Q5TAN8; Q9BZ25; Q9BZ26; Q9BZ27;
AC   Q9BZ28; Q9UPU4;
DT   19-OCT-2002, integrated into UniProtKB/Swiss-Prot.
DT   19-OCT-2002, sequence version 2.
DT   07-MAR-2006, entry version 39.
DE   Dedicator of cytokinesis protein 9 (Cdc42 guanine nucleotide exchange
DE   factor zizimin 1).
GN   Name=DOCK9; Synonyms=KIAA1058;
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae;
OC   Homo.
OX   NCBI_TaxID=9606;
RN   [1]
RP   NUCLEOTIDE SEQUENCE (ISOFORM 1), FUNCTION, INTERACTION WITH CDC42, GEF
RP   ACTIVITY, AND TISSUE SPECIFICITY.
RX   MEDLINE=22194783; PubMed=12172552; DOI=10.1038/ncb835;
RA   Meller N., Irani-Tehrani M., Kiosses W.B., Del Pozo M.A.,
RA   Schwartz M.A.;
RT   "Zizimin1, a novel Cdc42 activator, reveals a new GEF domain for Rho
RT   proteins.";
RL   Nat. Cell Biol. 4:639-647(2002).
RN   [2]
RP   NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA] (ISOFORM 2).
RC   TISSUE=Brain;
RX   MEDLINE=99397452; PubMed=10470851; DOI=10.1093/dnares/6.3.197;
RA   Kikuno R., Nagase T., Ishikawa K., Hirosawa M., Miyajima N.,
RA   Tanaka A., Kotani H., Nomura N., Ohara O.;
RT   "Prediction of the coding sequences of unidentified human genes. XIV.
RT   The complete sequences of 100 new cDNA clones from brain which code
RT   for large proteins in vitro.";
RL   DNA Res. 6:197-205(1999).
RN   [3]
RP   SEQUENCE REVISION.
RX   MEDLINE=22158633; PubMed=12168954; DOI=10.1093/dnares/9.3.99;
RA   Nakajima D., Okazaki N., Yamakawa H., Kikuno R., Ohara O., Nagase T.;
RT   "Construction of expression-ready cDNA clones for KIAA genes: manual
RT   curation of 330 KIAA cDNA clones.";
RL   DNA Res. 9:99-106(2002).
RN   [4]
RP   NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA] (ISOFORMS 1; 2; 3 AND
RP   4).
RX   PubMed=15057823; DOI=10.1038/nature02379;
RA   Dunham A., Matthews L.H., Burton J., Ashurst J.L., Howe K.L.,
RA   Ashcroft K.J., Beare D.M., Burford D.C., Hunt S.E.,
RA   Griffiths-Jones S., Jones M.C., Keenan S.J., Oliver K., Scott C.E.,
RA   Ainscough R., Almeida J.P., Ambrose K.D., Andrews D.T.,
RA   Ashwell R.I.S., Babbage A.K., Bagguley C.L., Bailey J., Bannerjee R.,
RA   Barlow K.F., Bates K., Beasley H., Bird C.P., Bray-Allen S.,
RA   Brown A.J., Brown J.Y., Burrill W., Carder C., Carter N.P.,
RA   Chapman J.C., Clamp M.E., Clark S.Y., Clarke G., Clee C.M.,
RA   Clegg S.C., Cobley V., Collins J.E., Corby N., Coville G.J.,
RA   Deloukas P., Dhami P., Dunham I., Dunn M., Earthrowl M.E.,
RA   Ellington A.G., Faulkner L., Frankish A.G., Frankland J., French L.,
RA   Garner P., Garnett J., Gilbert J.G.R., Gilson C.J., Ghori J.,
RA   Grafham D.V., Gribble S.M., Griffiths C., Hall R.E., Hammond S.,
RA   Harley J.L., Hart E.A., Heath P.D., Howden P.J., Huckle E.J.,
RA   Hunt P.J., Hunt A.R., Johnson C., Johnson D., Kay M., Kimberley A.M.,
RA   King A., Laird G.K., Langford C.J., Lawlor S., Leongamornlert D.A.,
RA   Lloyd D.M., Lloyd C., Loveland J.E., Lovell J., Martin S.,
RA   Mashreghi-Mohammadi M., McLaren S.J., McMurray A., Milne S.,
RA   Moore M.J.F., Nickerson T., Palmer S.A., Pearce A.V., Peck A.I.,
RA   Pelan S., Phillimore B., Porter K.M., Rice C.M., Searle S.,
RA   Sehra H.K., Shownkeen R., Skuce C.D., Smith M., Steward C.A.,
RA   Sycamore N., Tester J., Thomas D.W., Tracey A., Tromans A., Tubby B.,
RA   Wall M., Wallis J.M., West A.P., Whitehead S.L., Willey D.L.,
RA   Wilming L., Wray P.W., Wright M.W., Young L., Coulson A., Durbin R.,
RA   Hubbard T., Sulston J.E., Beck S., Bentley D.R., Rogers J., Ross M.T.;
RT   "The DNA sequence and analysis of human chromosome 13.";
RL   Nature 428:522-528(2004).
RN   [5]
RP   NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA] OF 1551-2069 (ISOFORM 4).
RC   TISSUE=Eye;
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Appendix A

```
RX   MEDLINE=22388257; PubMed=12477932; DOI=10.1073/pnas.242603899;
RA   Strausberg R.L., Feingold E.A., Grouse L.H., Derge J.G.,
RA   Klausner R.D., Collins F.S., Wagner L., Shenmen C.M., Schuler G.D.,
RA   Altschul S.F., Zeeberg B., Buetow K.H., Schaefer C.F., Bhat N.K.,
RA   Hopkins R.F., Jordan H., Moore T., Max S.I., Wang J., Hsieh F.,
RA   Diatchenko L., Marusina K., Farmer A.A., Rubin G.M., Hong L.,
RA   Stapleton M., Soares M.B., Bonaldo M.F., Casavant T.L., Scheetz T.E.,
RA   Brownstein M.J., Usdin T.B., Toshiyuki S., Carninci P., Prange C.,
RA   Raha S.S., Loquellano N.A., Peters G.J., Abramson R.D., Mullahy S.J.,
RA   Bosak S.A., McEwan P.J., McKernan K.J., Malek J.A., Gunaratne P.H.,
RA   Richards S., Worley K.C., Hale S., Garcia A.M., Gay L.J., Hulyk S.W.,
RA   Villalon D.K., Muzny D.M., Sodergren E.J., Lu X., Gibbs R.A.,
RA   Fahey J., Helton E., Ketteman M., Madan A., Rodrigues S., Sanchez A.,
RA   Whiting M., Madan A., Young A.C., Shevchenko Y., Bouffard G.G.,
RA   Blakesley R.W., Touchman J.W., Green E.D., Dickson M.C.,
RA   Rodriguez A.C., Grimwood J., Schmutz J., Myers R.M.,
RA   Butterfield Y.S.N., Krzywinski M.I., Skalska U., Smailus D.E.,
RA   Schnerch A., Schein J.E., Jones S.J.M., Marra M.A.;
RT   "Generation and initial analysis of more than 15,000 full-length human
RT   and mouse cDNA sequences.";
RL   Proc. Natl. Acad. Sci. U.S.A. 99:16899-16903(2002).
RN   [6]
RP   NOMENCLATURE, AND GEF ACTIVITY.
RX   MEDLINE=22319137; PubMed=12432077; DOI=10.1242/jcs.00219;
RA   Cote J.-F., Vuori K.;
RT   "Identification of an evolutionarily conserved superfamily of DOCK180-
RT   related proteins with guanine nucleotide exchange activity.";
RL   J. Cell Sci. 115:4901-4913(2002).
CC   -!- FUNCTION: Guanine nucleotide-exchange factor (GEF) that activates
CC       CDC42 by exchanging bound GDP for free GTP. Overexpression induces
CC       filopodia formation.
CC   -!- SUBUNIT: Interacts preferentially with nucleotide-depleted CDC42.
CC   -!- SUBCELLULAR LOCATION: Cytoplasmic; associated with membranes
CC       (Probable).
CC   -!- ALTERNATIVE PRODUCTS:
CC       Event=Alternative splicing; Named isoforms=4;
CC       Name=1;
CC         IsoId=Q9BZ29-1; Sequence=Displayed;
CC       Name=2;
CC         IsoId=Q9BZ29-5; Sequence=VSP_017128;
CC       Name=3;
CC         IsoId=Q9BZ29-3; Sequence=VSP_004024;
CC         Note=No experimental confirmation available;
CC       Name=4;
CC         IsoId=Q9BZ29-4; Sequence=VSP_007709, VSP_007710;
CC         Note=Produced by exon skipping that results in a frameshift. No
CC         experimental confirmation available;
CC   -!- TISSUE SPECIFICITY: Widely expressed, with highest expression in
CC       heart and placenta. Expressed at intermediate level in kidney,
CC       brain, lung and skeletal muscle.
CC   -!- DOMAIN: The DHR-2 domain is necessary and sufficient for the GEF
CC       activity.
CC   -!- MISCELLANEOUS: 'Zizim' means 'spike' in Hebrew.
CC   -!- SIMILARITY: Belongs to the DOCK family.
CC   -!- SIMILARITY: Contains 1 DHR-1 (CZH-1) domain.
CC   -!- SIMILARITY: Contains 1 DHR-2 (CZH-2) domain.
CC   -!- SIMILARITY: Contains 1 PH domain.
CC   ---------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   ---------------------------------------------------------------------
DR   EMBL; AF527605; AAM90306.1; -; mRNA.
DR   EMBL; AB028981; BAA83010.2; ALT_INIT; mRNA.
DR   EMBL; AL139084; CAI13370.1; -; Genomic_DNA.
DR   EMBL; AL161420; CAI13370.1; JOINED; Genomic_DNA.
DR   EMBL; AL139084; CAI13372.1; -; Genomic_DNA.
DR   EMBL; AL161420; CAI13372.1; JOINED; Genomic_DNA.
DR   EMBL; AL391122; CAI13372.1; JOINED; Genomic_DNA.
DR   EMBL; AL161420; CAI39569.1; -; Genomic_DNA.
DR   EMBL; AL139084; CAI39569.1; JOINED; Genomic_DNA.
DR   EMBL; AL161420; CAI39570.1; -; Genomic_DNA.
DR   EMBL; AL161420; CAI39574.1; -; Genomic_DNA.
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DR   EMBL; AL391122; CAI39574.1; JOINED; Genomic_DNA.
DR   EMBL; AL161420; CAI39577.1; -; Genomic_DNA.
DR   EMBL; AL391122; CAI11061.1; -; Genomic_DNA.
```

Appendix A

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DR   EMBL; AL139084; CAI11061.1; JOINED; Genomic_DNA.
DR   EMBL; AL161420; CAI11061.1; JOINED; Genomic_DNA.
DR   EMBL; BC043506; AAH43506.1; -; mRNA.
DR   PDB; 1WG7; NMR; A=165-301.
DR   Ensembl; ENSG00000088387; Homo sapiens.
DR   HGNC; HGNC:14132; DOCK9.
DR   MIM; 607325; gene.
DR   LinkHub; Q9BZ29; -.
DR   InterPro; IPR010703; DOCK.
DR   InterPro; IPR001849; PH.
DR   InterPro; IPR011993; PH_type.
DR   Pfam; PF06920; Ded_cyto; 1.
DR   Pfam; PF00169; PH; 1.
DR   SMART; SM00233; PH; 1.
DR   PROSITE; PS50003; PH_DOMAIN; 1.
KW   3D-structure; Alternative splicing; Coiled coil;
KW   Guanine-nucleotide releasing factor; Repeat.
FT   CHAIN         1   2069       Dedicator of cytokinesis protein 9.
FT                                /FTId=PRO_0000189999.
FT   DOMAIN      174    281       PH.
FT   DOMAIN      641    879       DHR-1.
FT   DOMAIN     1505   2060       DHR-2.
FT   COILED     1948   1982       Potential.
FT   COILED     2034   2067       Potential.
FT   VARSPLIC      1     43       MSQPPLLPASAETRKFTRALSKPGTAAELRQSVSEVVRGSV
FT                                LL -> MQADKCRTSSRSVKKELVIESPLQYKDAAQGEVEA
FT                                ESPGPVP (in isoform 2).
FT                                /FTId=VSP_017128.
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FT                                DNG (in isoform 3).
FT                                /FTId=VSP_004024.
FT   VARSPLIC   1791   1804       Missing (in isoform 4).
FT                                /FTId=VSP_007709.
FT   VARSPLIC   2068   2069       LG -> ICPLEEKTSVLPNSLHIFNAISGTPTSTMVHGMTS
FT                                SSSVV (in isoform 4).
FT                                /FTId=VSP_007710.
FT   STRAND      170    170
FT   STRAND      172    172
FT   STRAND      178    183
FT   STRAND      188    189
FT   HELIX       190    194
FT   STRAND      195    196
FT   STRAND      198    206
FT   STRAND      208    210
FT   STRAND      212    220
FT   STRAND      223    224
FT   STRAND      227    230
FT   TURN        232    234
FT   STRAND      237    238
FT   STRAND      243    244
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Query Match 94.0%; Score 6584.5; DB 1; Length 2069;
Best Local Similarity 92.4%; Pred. No. 0;
Matches 1285; Conservative 2; Mismatches 3; Indels 101; Gaps 3;

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Qy          1 VLHHHQNPEFYDEIKIELPTQLHEKHHLLLTFFHVSCDNSSKGSTKKRDVVETQVGYSWL 60
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Db        701 VLHHHQNPEFYDEIKIELPTQLHEKHHLLLTFFHVSCDNSSKGSTKKRDVVETQVGYSWL 760

Qy         61 PLLKDGRVVTSEQHIPVSANLPSGYLGYQELGMGRHYGPEIKWVDGGKPLLKISTHLVST 120
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Db        761 PLLKDGRVVTSEQHIPVSANLPSGYLGYQELGMGRHYGPEIKWVDGGKPLLKISTHLVST 820

Qy        121 VYTQDQHLHNFFQYCQKTESGAQALGNELVKYLKSLHAMEGHVMIAFLPTILNQLFRVLT 180
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Qy        181 RATQEEVAVNVTRVIIHVVAQCHEEGLESHLRSYVKYAYKAEPYVASEYKTVHEELTKSM 240
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Qy        241 TTILKPSADFLTSNKLLRYSWFFFDVLIKSMAQHLIENSKVKLLRNQRFPASYHHAAETV 300
              ||||||||||||||||:|||||||||||||||||||||||||||||||||||| |||
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Qy        301 VNMLMPHITQKFGDNPEASKNANHSLAVFIKRCFTFMDRGFVFKQINNYISCFAPGDPKT 360
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Appendix A

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Qy        361 LFEYKFEFLRVVCNHEHYIPLNLPMPFGKGRIQRYQDLQLDYSLTDEFCRNHFLVGLLLR 420
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Qy        421 EVGTALQEFREVRLIAISVLKNLLIKHSFDDRYASRSHQARIATLYLPLFGLLIENVQRI 480
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Qy        481 NVRDVSPFPVNAGMTVKDESLALPAVNPLVTPQKGSTLDNSLHKDLLGAISGIASPYTTS 540
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Qy        541 TPNINSVRNADSRGSLISTDSGNSLPERNSEKSNSLDKHQQSSTLGNSVVRCDKLDQSEI 600
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Qy        601 KSLLMCFLYILKSMSDDALFTYWNKASTSELMDFFTISEVCLHQFQYMGKRYIARNQEGL 660
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Db       1301 KSLLMCFLYILKSMSDDALFTYWNKASTSELMDFFTISEVCLHQFQYMGKRYIA------ 1354

Qy        661 GPIVHDRKSQTLPVSRNRTGMMHARLQQLGSLDNSLTFNHSYGHSDADVLHQSLLEANIA 720
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Db       1355 ----------------RTGMMHARLQQLGSLDNSLTFNHSYGHSDADVLHQSLLEANIA 1397

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Qy        781 SLIYKFPSTFYEGRADMCAALCYEILKCCNSKLSSIRTEASQLLYFLMRNNFDYTGKKSF 840
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy       1051 ----------------------------------------------FFEDEDGKEYIY 1062
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Qy       1063 KEPKLTPLSEISQRLLKLYSDKFGSENVKMIQDSGKVNPKDLDSKYAYIQVTHVIPFFDE 1122
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Qy       1123 KELQERKTEFERSHNIRRFMFEMPFTQTGKRQGGVEEQCKRRTILTAIHCFPYVKKRIPV 1182
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Appendix B

<!--StartFragment-->RESULT 2
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LOCUS DQ047772 6195 bp DNA linear GSS 02-JUN-2005
DEFINITION Homo sapiens ZIZIMIN1 gene, VIRTUAL TRANSCRIPT, partial sequence, genomic survey sequence.
ACCESSION DQ047772
VERSION DQ047772.1 GI:66900971
KEYWORDS GSS.
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 6195)
AUTHORS Nielsen,R., Bustamante,C., Clark,A.G., Glanowski,S., Sackton,T.B., Hubisz,M.J., Fledel-Alon,A., Tanenbaum,D.M., Civello,D., White,T.J., Sninsky,J.J., Adams,M.D. and Cargill,M.
TITLE A Scan for Positively Selected Genes in the Genomes of Humans and Chimpanzees
JOURNAL (er) PLoS Biol. 3 (6), E170 (2005)
PUBMED 15869325
REFERENCE 2 (bases 1 to 6195)
AUTHORS Nielsen,R., Bustamante,C., Clark,A.G., Glanowski,S., Sackton,T.B., Hubisz,M.J., Fledel-Alon,A., Tanenbaum,D.M., Civello,D., White,T.J., Sninsky,J.J., Adams,M.D. and Cargill,M.
TITLE Direct Submission
JOURNAL Submitted (05-MAY-2005) Celera Genomics, 45 West Gude Drive, Rockville, MD 20850, USA
COMMENT This sequence was made by sequencing genomic exons and ordering them based on alignment. Translation starts at the beginning of alignment.
FEATURES Location/Qualifiers
source 1. .6195
/organism="Homo sapiens"
/mol_type="genomic DNA"
/db_xref="taxon:9606"
/chromosome="13"
gene <1. .>6195
/gene="ZIZIMIN1"
/locus_tag="HC15707"
ORIGIN

Query Match 73.8%; Score 3547.4; DB 14; Length 6195;
Best Local Similarity 90.4%; Pred. No. 0;
Matches 3878; Conservative 0; Mismatches 113; Indels 297; Gaps 3;

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Qy          1 AGTTTTACACCATCACCAAAACCCAGAATTTTATGATGAGATTAAAATAGAGTTGCCCAC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1977 AGTTTTACACCATCACCAAAACCCAGAATTTTATGATGAGATTAAAATAGAGTTGCCCAC 2036

Qy         61 TCAGCTGCATGAAAAGCACCACCTGTTGCTCACATTCTTCCATGTCAGCTGTGACAACTC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2037 TCAGCTGCATGAAAAGCACCACCTGTTGCTCACATTCTTCCATGTCAGCTGTGACAACTC 2096

Qy        121 AAGTAAAGGAAGCACGAAGAAGAGGGATGTCGTTGAAACCCAAGTTGGCTACTCCTGGCT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2097 AAGTAAAGGAAGCACGAAGAAGAGGGATGTCGTTGAAACCCAAGTTGGCTACTCCTGGCT 2156

Qy        181 TCCCCTCCTGAAAGACGGAAGGGTGGTGACAAGCGAGCAGCACATCCCGGTCTCGGCGAA 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2157 TCCCCTCCTGAAAGACGGAAGGGTGGTGACAAGCGAGCAGCACATCCCGGTCTCGGCGAA 2216

Qy        241 CCTTCCTTCGGGCTATCTTGGCTACCAAGAGCTTGGGATGGGCAGGCATTATGGTCCGGA 300
              |||||||||||||||||||||||||| ||||||||||||||||||||||||||||||||
Db       2217 CCTTCCTTCGGGCTATCTTGGCTACCAGGAGCTTGGGATGGGCAGGCATTATGGTCCGGA 2276

Qy        301 AATTAAATGGGTAGATGGAGGCAAGCCACTGCTGAAAATTTCCACTCATCTGGTTTCTAC 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2277 AATTAAATGGGTAGATGGAGGCAAGCCACTGCTGAAAATTTCCACTCATCTGGTTTCTAC 2336

Qy        361 AGTGTATACTCAGGATCAGCATTTACATAATTTTTTCCAGTACTGTCAGAAAACCGAATC 420
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Db       2337 AGTGTATACTCAGGATCAGCATTTACATAATTTTTTCCAGTACTGTCAGAAAACCGAATC 2396

Qy        421 TGGAGCCCAAGCCTTAGGAAACGAACTTGTAAAGTACCTTAAGAGTCTGCATGCGATGGA 480
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Appendix B

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            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy       541 CAGAGCCACACAGGAAGAAGTCGCGGTTAACGTGACTCGGGTCATTATTCATGTGGTTGC 600
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Qy       601 CCAGTGCCATGAGGAAGGATTGGAGAGCCACTTGAGGTCATATGTTAAGTACGCGTATAA 660
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2577 CCAGTGCCATGAGGAAGGATTGGAGAGCCACTTGAGGTCATATGTTAAGTACGCGTATAA 2636

Qy       661 GGCTGAGCCATATGTTGCCTCTGAATACAAGACAGTGCATGAAGAACTGACCAAATCCAT 720
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2637 GGCTGAGCCATATGTTGCCTCTGAATACAAGACAGTGCATGAAGAACTGACCAAATCCAT 2696

Qy       721 GACCACGATTCTCAAGCCTTCTGCCGATTTCCTCACCAGCAACAAACTACTGAGGTACTC 780
            |||||||||||||||||||||||||||||||||||||||||||||||||||| ||||||
Db      2697 GACCACGATTCTCAAGCCTTCTGCCGATTTCCTCACCAGCAACAAACTACTGAAGTACTC 2756

Qy       781 ATGGTTTTTCTTTGATGTACTGATCAAATCTATGGCTCAGCATTTGATAGAGAACTCCAA 840
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2757 ATGGTTTTTCTTTGATGTACTGATCAAATCTATGGCTCAGCATTTGATAGAGAACTCCAA 2816

Qy       841 AGTTAAGTTGCTGCGAAACCAGAGATTTCCTGCATCCTATCATCATGCAGCGGAAACCGT 900
            |||||||||||||||||||||||||||||||||||||||||||||||||| |||||||||
Db      2817 AGTTAAGTTGCTGCGAAACCAGAGATTTCCTGCATCCTATCATCATGCAGTGGAAACCGT 2876

Qy       901 TGTAAATATGCTGATGCCACACATCACTCAGAAGTTTGGAGATAATCCAGAGGCATCTAA 960
            |||||||||||||||||||||||||||||||||| ||||||||||||||||||||||||
Db      2877 TGTAAATATGCTGATGCCACACATCACTCAGAAGTTTCGAGATAATCCAGAGGCATCTAA 2936

Qy       961 GAACGCGAATCATAGCCTTGCTGTCTTCATCAAGAGATGTTTCACCTTCATGGACAGGGG 1020
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2937 GAACGCGAATCATAGCCTTGCTGTCTTCATCAAGAGATGTTTCACCTTCATGGACAGGGG 2996

Qy      1021 CTTTGTCTTCAAGCAGATCAACAACTACATTAGCTGTTTTGCTCCTGGAGACCCAAAGAC 1080
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2997 CTTTGTCTTCAAGCAGATCAACAACTACATTAGCTGTTTTGCTCCTGGAGACCCAAAGAC 3056

Qy      1081 CCTCTTTGAATACAAGTTTGAATTTCTCCGTGTAGTGTGCAACCATGAACATTATATTCC 1140
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3057 CCTCTTTGAATACAAGTTTGAATTTCTCCGTGTAGTGTGCAACCATGAACATTATATTCC 3116

Qy      1141 GTTGAACTTACCAATGCCATTTGGAAAAGGCAGGATTCAAAGATACCAAGACCTCCAGCT 1200
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3117 GTTGAACTTACCAATGCCATTTGGAAAAGGCAGGATTCAAAGATACCAAGACCTCCAGCT 3176

Qy      1201 TGACTACTCATTAACAGATGAGTTCTGCAGAAACCACTTCTTGGTGGGACTGTTACTGAG 1260
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3177 TGACTACTCATTAACAGATGAGTTCTGCAGAAACCACTTCTTGGTGGGACTGTTACTGAG 3236

Qy      1261 GGAGGTGGGGACAGCCCTCCAGGAGTTCCGGGAGGTCCGTCTGATCGCCATCAGTGTGCT 1320
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3237 GGAGGTGGGGACAGCCCTCCAGGAGTTCCGGGAGGTCCGTCTGATCGCCATCAGTGTGCT 3296

Qy      1321 CAAGAACCTGCTGATAAAGCATTCTTTTGATGACAGATATGCTTCAAGGAGCCATCAGGC 1380
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3297 CAAGAACCTGCTGATAAAGCATTCTTTTGATGACAGATATGCTTCAAGGAGCCATCAGGC 3356

Qy      1381 AAGGATAGCCACCCTCTACCTGCCTCTGTTTGGTCTGCTGATTGAAAACGTCCAGCGGAT 1440
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3357 AAGGATAGCCACCCTCTACCTGCCTCTGTTTGGTCTGCTGATTGAAAACGTCCAGCGGAT 3416

Qy      1441 CAATGTGAGGGATGTGTCACCCTTCCCTGTGAACGCGGGCATGACCGTGAAGGATGAATC 1500
            |||||||||||||||||||||||||||||||||||||||||||| ||||||||||||||
Db      3417 CAATGTGAGGGATGTGTCACCCTTCCCTGTGAACGCGGGCATGACTGTGAAGGATGAATC 3476

Qy      1501 CCTGGCTCTACCAGCTGTGAATCCGCTGGTGACGCCGCAGAAGGGAAGCACCCTGGACAA 1560
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      3477 CCTGGCTCTACCAGCTGTGAATCCGCTGGTGACGCCGCAGAAGGGAAGCACCCTGGACAA 3536

Qy      1561 CAGCCTGCACAAGGACCTGCTGGGCGCCATCTCCGGCATTGCTTCTCCATATACAACCTC 1620
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Appendix B

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Db       3537 CAGCCTGCACAAGGACCTGCTGGGCGCCATCTCCGGCATTGCTTCTCCATATACAACCTC 3596

Qy       1621 AACTCCAAACATCAACAGTGTGAGAAATGCTGATTCGAGAGGATCTCTCATAAGCACAGA 1680
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3597 AACTCCAAACATCAACAGTGTGAGAAATGCTGATTCGAGAGGATCTCTCATAAGCACAGA 3656

Qy       1681 TTCGGGTAACAGCCTTCCAGAAAGGAATAGTGAGAAGAGCAATTCCCTGGATAAGCACCA 1740
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3657 TTCGGGTAACAGCCTTCCAGAAAGGAATAGTGAGAAGAGCAATTCCCTGGATAAGCACCA 3716

Qy       1741 ACAAAGTAGCACATTGGGAAATTCCGTGGTTCGCTGTGATAAACTTGACCAGTCTGAGAT 1800
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3717 ACAAAGTAGCACATTGGGAAATTCCGTGGTTCGCTGTGATAAACTTGACCAGTCTGAGAT 3776

Qy       1801 TAAGAGCCTACTGATGTGTTTCCTCTACATCTTAAAGAGCATGTCTGATGATGCTTTGTT 1860
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3777 TAAGAGCCTACTGATGTGTTTCCTCTACATCTTAAAGAGCATGTCTGATGATGCTTTGTT 3836

Qy       1861 TACATATTGGAACAAGGCTTCAACATCTGAACTTATGGATTTTTTTACAATATCTGAAGT 1920
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3837 TACATATTGGAACAAGGCTTCAACATCTGAACTTATGGATTTTTTTACAATATCTGAAGT 3896

Qy       1921 CTGCCTGCACCAGTTCCAGTACATGGGGAAGCGATACATAGCCAGGAACCAGGAGGGGTT 1980
              |||||||||||||||||||||||||||||||||||||||
Db       3897 CTGCCTGCACCAGTTCCAGTACATGGGGAAGCGATACATAGC---------------------- 3938

Qy       1981 GGGACCCATAGTTCATGATCGAAAGTCTCAGACATTGCCTGTTTCCCGTAACAGAACAGG 2040
                                                                 |||||||||
Db       3939 ----------------------------------------------------CAGAACAGG 3947

Qy       2041 AATGATGCATGCCAGATTGCAGCAGCTGGGCAGCCTGGATAACTCTCTCACTTTTAACCA 2100
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3948 AATGATGCATGCCAGATTGCAGCAGCTGGGCAGCCTGGATAACTCTCTCACTTTTAACCA 4007

Qy       2101 CAGCTATGGCCACTCGGACGCAGATGTTCTGCACCAGTCATTACTTGAAGCCAACATTGC 2160
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4008 CAGCTATGGCCACTCGGACGCAGATGTTCTGCACCAGTCATTACTTGAAGCCAACATTGC 4067

Qy       2161 TACTGAGGTTTGCCTGACAGCTCTGGACACGCTTTCTCTATTTACATTGGCGTTTAAGAA 2220
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4068 TACTGAGGTTTGCCTGACAGCTCTGGACACGCTTTCTCTATTTACATTGGCGTTTAAGAA 4127

Qy       2221 CCAGCTCCTGGCCGACCATGGACATAATCCTCTCATGAAAAAAGTTTTTGATGTCTACCT 2280
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4128 CCAGCTCCTGGCCGACCATGGACATAATCCTCTCATGAAAAAAGTTTTTGATGTCTACCT 4187

Qy       2281 GTGTTTTCTTCAAAAACATCAGTCTGAAACGGCTTTAAAAAATGTCTTCACTGCCTTAAG 2340
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4188 GTGTTTTCTTCAAAAACATCAGTCTGAAACGGCTTTAAAAAATGTCTTCACTGCCTTAAG 4247

Qy       2341 GTCCTTAATTTATAAGTTTCCCTCAACATTCTATGAAGGGAGAGCGGACATGTGTGCGGC 2400
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4248 GTCCTTAATTTATAAGTTTCCCTCAACATTCTATGAAGGGAGAGCGGACATGTGTGCGGC 4307

Qy       2401 TCTGTGTTACGAGATTCTCAAGTGCTGTAACTCCAAGCTGAGCTCCATCAGGACGGAGGC 2460
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4308 TCTGTGTTACGAGATTCTCAAGTGCTGTAACTCCAAGCTGAGCTCCATCAGGACGGAGGC 4367

Qy       2461 CTCCCAGCTGCTCTACTTCCTGATGAGGAACAACTTTGATTACACTGGAAAGAAGTCCTT 2520
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4368 CTCCCAGCTGCTCTACTTCCTGATGAGGAACAACTTTGATTACACTGGAAAGAAGTCCTT 4427

Qy       2521 TGTCCGGACACATTTGCAAGTCATCATATCTGTCAGCCAGCTGATAGCAGACGTTGTTGG 2580
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4428 TGTCCGGACACATTTGCAAGTCATCATATCTGTCAGCCAGCTGATAGCAGACGTTGTTGG 4487

Qy       2581 CATTGGGGAAACCAGATTCCAGCAGTCCCTGTCCATCATCAACAACTGTGCCAACAGTGA 2640
              |||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4488 CATTGGGGGAACCAGATTCCAGCAGTCCCTGTCCATCATCAACAACTGTGCCAACAGTGA 4547

Qy       2641 CCGGCTTATTAAGCACACCAGCTTCTCCTCTGATGTGAAGGACTTAACCAAAAGGATACG 2700
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4548 CCGGCTTATTAAGCACACCAGCTTCTCCTCTGATGTGAAGGACTTAACCAAAAGGATACG 4607

Qy       2701 CACGGTGCTAATGGCCACCGCCCAGATGAAGGAGCATGAGAACGACCCAGAGATGCTGGT 2760
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db       4608 CACGGTGCTAATGGCCACCGCCCAGATGAAGGAGCATGAGAACGACCCAGAGATGCTGGT 4667

Qy       2761 GGACCTCCAGTACAGCCTGGCCAAATCCTATGCCAGCACGCCCGAGCTCAGGAAGACGTG 2820
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4668 GGACCTCCAGTACAGCCTGGCCAAATCCTATGCCAGCACGCCCGAGCTCAGGAAGACGTG 4727

Qy       2821 GCTCGACAGCATGGCCAGGATCCATGTCAAAAATGGCGATCTCTCAGAGGCAGCAATGTG 2880
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4728 GCTCGACAGCATGGCCAGGATCCATGTCAAAAATGGCGATCTCTCAGAGGCAGCAATGTG 4787

Qy       2881 CTATGTCCACGTAACAGCCCTAGTGGCAGAATATCTCACACGGAA---------------- 2925
             |||||||||||||||||||||||||||||||||||||||||||||
Db       4788 CTATGTCCACGTAACAGCCCTAGTGGCAGAATATCTCACACGGAAAGAAGCAGTCCAGTG 4847

Qy       2926 ----------------------------------------------------AGGCGT 2931
                                                                    ||
Db       4848 GGAGCCGCCCCTTCTCCCCCACAGCCATAGCGCCTGCCTGAGGAGGAGCCGGGGAGNNNN 4907

Qy       2932 GTTTAGACAAGGATGCACCGCCTTCAGGGTCATTACCCCAAACATCGACGAGGAGGCCTC 2991

Db       4908 NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN 4967

Qy       2992 CATGATGGAAGACGTGGGGATGCAGGATGTCCATTTCAACGAGGATGTGCTGATGGAGCT 3051
                                                   ||||||||||||||||
Db       4968 NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNGATGTGCTGATGGAGCT 5027

Qy       3052 CCTTGAGCAGTGCGCAGATGGACTCTGGAAAGCCGAGCGCTACGAGCTCATCGCCGACAT 3111
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5028 CCTTGAGCAGTGCGCAGATGGACTCTGGAAAGCCGAGCGCTACGAGCTCATCGCCGACAT 5087

Qy       3112 CTACAAACTTATCATCCCCATTTATGAGAAGCGGAGGGAT-------------------- 3151
             |||||||||||||||||||||||||||||||||||||||
Db       5088 CTACAAACTTATCATCCCCATTTATGAGAAGCGGAGGGATTTTGAGAGGCTGGCCCATCT 5147

Qy       3152 ------------------------------------------------------------ 3151

Db       5148 GTATGACACGCTGCACCGGGCCTACAGCAAAGTGACCGAGGTCATGCACTCGGGCCGCAG 5207

Qy       3152 ------------------------------------------------------------ 3151

Db       5208 GCTTCTGGGGACCTACTTCCGGGTAGCCTTCTTCGGGCAGCAATACCAGTTTACAGACAG 5267

Qy       3152 --------------------TTCTTTGAAGATGAAGATGGAAAGGAGTATATTTACAAGGA 3192
                                    ||||||||||||||||||||||||||||||||||||||||
Db       5268 TGAAACAGATGTGGAGGGATTCTTTGAAGATGAAGATGGAAAGGAGTATATTTACAAGGA 5327

Qy       3193 ACCCAAACTCACACCGCTGTCGGAAATTTCTCAGAGACTCCTTAAACTGTACTCGGATAA 3252
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5328 ACCCAAACTCACACCGCTGTCGGAAATTTCTCAGAGACTCCTTAAACTGTACTCGGATAA 5387

Qy       3253 ATTTGGTTCTGAAAATGTCAAAATGATACAGGATTCTGGCAAGGTCAACCCTAAGGATCT 3312
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5388 ATTTGGTTCTGAAAATGTCAAAATGATACAGGATTCTGGCAAGGTCAACCCTAAGGATCT 5447

Qy       3313 GGATTCTAAGTATGCATACATCCAGGTGACTCACGTCATCCCCTTCTTTGACGAAAAAGA 3372
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5448 GGATTCTAAGTATGCATACATCCAGGTGACTCACGTCATCCCCTTCTTTGACGAAAAAGA 5507

Qy       3373 GTTGCAAGAAAGGAAAACAGAGTTTGAGAGATCCCACAACATCCGCCGCTTCATGTTTGA 3432
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5508 GTTGCAAGAAAGGAAAACAGAGTTTGAGAGATCCCACAACATCCGCCGCTTCATGTTTGA 5567

Qy       3433 GATGCCATTTACGCAGACCGGGAAGAGGCAGGGCGGGGTGGAAGAGCAGTGCAAACGGCG 3492
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5568 GATGCCATTTACGCAGACCGGGAAGAGGCAGGGCGGGGTGGAAGAGCAGTGCAAACGGCG 5627

Qy       3493 CACCATCCTGACAGCCATACACTGCTTCCCTTATGTGAAGAAGCGCATCCCTGTCATGTA 3552
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5628 CACCATCCTGACAGCCATACACTGCTTCCCTTATGTGAAGAAGCGCATCCCTGTCATGTA 5687

Qy       3553 CCAGCACCACACTGACCTGAACCCCATCGAGGTGGCCATTGACGAGATGAGTAAGAAGGT 3612
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5688 CCAGCACCACACTGACCTGAACCCCATCGAGGTGGCCATTGACGAGATGAGTAAGAAGGT 5747

Qy       3613 GGCGGAGCTCCGGCAGCTGTGCTCCTCGGCCGAGGTGGACATGATCAAACTGCAGCTCAA 3672
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db       5748 GGCGGAGCTCCGGCAGCTGTGCTCCTCGGCCGAGGTGGACATGATCAAACTGCAGCTCAA 5807

Qy       3673 ACTCCAGGGCAGCGTGAGTGTTCAGGTCAATGCTGGCCCACTAGCATATGCGCGAGCTTT 3732
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5808 ACTCCAGGGCAGCGTGAGTGTTCAGGTCAATGCTGGCCCACTAGCATATGCGCGAGCTTT 5867

Qy       3733 CTTAGATGATACAAACACAAAGCGATATCCTGACAATAAAGTGAAGCTGCTTAAGGAAGT 3792
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5868 CTTAGATGATACAAACACAAAGCGATATCCTGACAATAAAGTGAAGCTGCTTAAGGAAGT 5927

Qy       3793 TTTCAGGCAATTTGTGGAAGCTTGCGGTCAAGCCTTAGCGGTAAACGAACGTCTGATTAA 3852
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5928 TTTCAGGCAATTTGTGGAAGCTTGCGGTCAAGCCTTAGCGGTAAACGAACGTCTGATTAA 5987

Qy       3853 AGAAGACCAGCTCGAGTATCAGGAAGAAATGAAAGCCAACTACAGGGAAATGGCGAAGGA 3912
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5988 AGAAGACCAGCTCGAGTATCAGGAAGAAATGAAAGCCAACTACAGGGAAATGGCGAAGGA 6047

Qy       3913 GCTTTCTGAAATCATGCATGAGCAGATCTGCCCCCTGGAGGAGAAGACGAGCGTCTTACC 3972
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6048 GCTTTCTGAAATCATGCATGAGCAGATCTGCCCCCTGGAGGAGAAGACGAGCGTCTTACC 6107

Qy       3973 GAATTCCCTTCACATCTTCAACGCCATCAGTGGGACTCCAACAAGCACAATGGTTCACGG 4032
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       6108 GAATTCCCTTCACATCTTCAACGCCATCAGTGGGACTCCAACAAGCACAATGGTTCACGG 6167

Qy       4033 GATGACCAGCTCGTCTTCGGTCGTGTGA 4060
              ||||||||||||||||||||||||||||
Db       6168 GATGACCAGCTCGTCTTCGGTCGTGTGA 6195
<!--EndFragment-->
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